

Appl. No.: 10/573,212
Amdt. Dated December 16, 2008
Reply to Office action of September 18, 2008

Amendments to the Claims:

1. (Previously Presented) A transgenic homozygous TRAM-knock out mouse non-responsive to endotoxin wherein a part or a whole of TRIF-related adaptor molecule (TRAM) genes on its chromosome is deleted, a function of expressing TRAM which is expressed in a wild-type is lacked, and responsiveness to a ligand recognized by TLR4 is specifically impaired.

2. (Previously Presented) The transgenic homozygous TRAM-knock out mouse non-responsive to endotoxin according to claim 1, which is responsive to PGN, R-848 and CpG ODN, and non-responsive to LPS.

3. (Cancelled)

4. (Currently Amended) A method for screening a substance promoting or suppressing a response to a ligand recognized by TLR4, wherein the following responses (a) to (c) to the ligand recognized by TLR4 in a immunocyte derived from the transgenic homozygous TRAM-knock out mouse non-responsive to endotoxin according to claim 1 or 2 is measured/estimated, with the use of the immunocyte, a test substance and the ligand recognized by TLR4:

- (a) cytokine (TNF α , IL-6 and IL-12p40) production of macrophage;
- (b) splenocyte proliferation, and up-regulation of surface molecules; and
- (c) expression of signaling molecules inducing IFN- β production.

5. (Currently Amended) A method for screening a substance promoting or suppressing a response to a ligand recognized by TLR4, wherein the following responses (a) to (c) to the ligand recognized by TLR4 in the transgenic homozygous TRAM-knock out mouse according to claim 1 or 2 is measured/estimated, with the use of the transgenic homozygous TRAM-knock out mouse, a test substance and the ligand recognized by TLR4:

- (a) cytokine (TNF α , IL-6 and IL-12p40) production of macrophage;
- (b) splenocyte proliferation, and up-regulation of surface molecules; and

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(c) expression of signaling molecules inducing IFN- β production.

6-7. (Cancelled)

8. (Previously Presented) An immunocyte from the transgenic homozygous TRAM-knock out mouse non-responsive to endotoxin according to claim 1 or 2.